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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,299	08/25/2006	Orit Kollet	30694/41506	2069

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MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 SEARS TOWER
CHICAGO, IL 60606-6357

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,299	KOLLET ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *1-29,37 and 40-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-36,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/29/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/552,299 filed on 08/25/2006 is a 371 of PCT/IL04/00314 filed on 04/07/2004, which claims the benefits of foreign applications ISRAEL 155302 filed on 04/08/2003 and ISRAEL 159306 filed on 12/10/2003.

Election/Restriction

Applicant's election with traverse of Group IX, drawn to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation, in the reply filed on 03/06/2009 is acknowledged. The traversal is on the ground(s) that (i) a special technical feature unifying the pending claims is use of matrix metalloprotease in methods of manipulating stem cells (See second paragraph, page 5 of Applicant's remark filed on 03/06/2009, and (ii) the Examiner must explain why each group lacks unity with each other group, specifically describing the unique special technical feature(s) of each group, and (iii) the Examiner failed to explain why, for example, the method of generating stem cells suitable for transplantation of claim 30 (Groups IX and X) is a different "invention" compared to the same method further comprising the step of determining homing capabilities of the stem cells, as recited in claim 40 (Groups XI and XII).

The traversal is not found persuasive because (i) the asserted special technical feature "use of matrix metalloprotease in methods of manipulating stem cells" unifying the pending claims does not exist the Groups directed to products (i.e. Groups XIII-XVII and XXVI), (ii)

comprehensive pair-wise comparisons between different Group of inventions are not germane to PCT lack of unity practice, as instant application is a 371 of PCT/IL04/00314 and (iii) Group IX is patentably distinct from Group X because the markers for identification of hematopoietic stem cells and potential differentiation lineages of hematopoietic stem cells of Group IX are patentably distinct from the markers for identification of hematopoietic stem cells and potential differentiation lineages of mesenchymal stem cells of Group X. Furthermore, the step of determining the homing capacities of Groups XI and XII are not obvious over the steps of isolating a given specified stem cells of Groups IX and X.

With regard to election of species, Applicant elects MMP-2 with traverse. The traversal is on the ground(s) that MMPs are characterized by a catalytic domain of about 170 amino acids including a zinc binding motif HE*XX*H*XX*G*XX*H and a conserved methionine, which forms a unique Met-turn structure. MMP-2 and MMP-9 further share three repeats of a fibronectin-type II domain inserted into the catalytic domain, which includes a five-stranded b-sheet, three a-helices, and bridging loops. The traversal is not found persuasive because, as stated on page 10 of restriction mailed on 02/06/2009, upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a). Nevertheless, upon further consideration, the requirement for election of species between MMP-2 and MMP-9 recited in claim 33 is withdrawn because further search indicates that MMP-2 and MMP-9 are obvious variants to each other (See, for

instance, **Skiles et al.**, The design, structure, and clinical update of small molecular weight matrix metalloproteinase inhibitors, *Curr Med Chem.* 11(22):2911-77, 2004).

Claims 1-62 are pending. Claims 1-29, 37, and 40-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03/06/2009.

Claims 30-36, 38, and 39 are currently under examination to the extent of hematopoietic stem cells.

The requirement is still deemed proper and is therefore made FINAL

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Claims 30-36, 38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 recites the limitation "isolating stem cells having CXCR4 levels above a predetermined threshold". The term "a predetermined threshold" is unclear because the metes and bounds of the limitation cannot be determined. The specification does not provide any definition of the term.

Claims 31-36, 38 and 39 depend from claim 30.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 30-36, 38, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by **Kollet et al.** (Kollet et al., Rapid and efficient homing of human CD34(+) CD38(/low) CXCR4(+) stem and progenitor cells to the bone marrow and spleen of NOD/SCID and NOD/SCID/B2m(null) mice, *Blood* 97(10):3283-91, 2001; this reference is listed as reference C35 in the IDS filed by Applicant on 01/29/2007) as evidenced by **Janowska-Wieczorek et al.** (Janowska-Wieczorek et al., Growth factors and cytokines upregulate gelatinase expression in bone marrow CD34(+) cells and their transmigration through reconstituted basement membrane, *Blood*, 93(10):3379-90, 1999; this reference is listed as reference C31 in the IDS filed by Applicant on 01/29/2007).

Claim 30 is directed to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation.

Claim interpretation: The limitation "having CXCR4 levels above a predetermined threshold" recited in claim 30 is interpreted as any level of CXCR4 expression because "a predetermined threshold" can be any level of CXCR4 expression. The limitation "exposing said stem cells to a matrix metalloprotease or an active portion thereof" recited in claim 30 reads on exposure to (i) any amount of a matrix metalloprotease expressed by either exogenous or endogenous nucleic acid molecule of collected stem cells, or (ii) any amount of matrix metalloprotease polypeptide added exogenously to the collected stem cells.

Kollet et al. teaches that during development hematopoietic stem cells migrate from the fetal liver into the bone marrow (BM) and continuously produce maturing hematopoietic cells that are released into the blood circulation. Hematopoietic stem cells are functionally defined, based on their ability to home to the BM microenvironment and to durably repopulate transplanted recipients with both myeloid and lymphoid cells (See Introduction, page 3283, Kollet et al., 2001).

With regard to step (a) of claim 30 and limitations of claims 34-36, Kollet et al. teaches isolation of CD34+ hematopoietic stem cells from human cord blood (CB) sample using the MACS cell isolation kit and MidiMacs columns. Isolated $CD34^{+}$ cells were either used immediately for homing experiments or after overnight incubation with RPMI supplemented with 10% fetal calf serum (FCS) and stem cell factor (SCF) (50 ng/mL). In both cases only primitive $CD34^{+}CD38^{-/low}$ cells homed in vivo. (See Materials and methods, left column, page 3284, Kollet et al., 2001).

With regard to step (c) of claim 30 and limitation of claim 39, Kollet et al. teaches that Enriched $CD34^+$ cells were further labeled with human specific monoclonal antibody (mAb) anti-CD34 FITC (Becton Dickinson, San Jose, CA) and anti-CD38 PE (Coulter, Miami, FL) and sorted for $CD34^+CD38^{-/low}$- or $CD34^+CD38^+$-purified subpopulations by $FACStar^+$ (See Materials and methods, left column, page 3284, Kollet et al., 2001), and homing of enriched human $CD34^+$ cells was inhibited by pretreatment with anti-CXCR4 antibodies, moreover, primitive $CD34^+CD38^{-/low}CXCR4^+$ cells also homed in response to a gradient of human stromal cell-derived factor 1 (SDF-1), directly injected into the bone marrow or spleen of nonirradiated NOD/SCID mice (See abstract, page 3283, Kollet et al., 2001).

With regard to collecting stem cell effected by mobilization procedure recited in claim 31, Kollet et al. teaches an homing assay in which human $CD34^+$-enriched cells were either labeled prior to transplantation with the fluorescent dye PKH26-GL (2 μL PKH26-GL were added to 1-10 $\times$ 10^6 $CD34^+$ cells in a total volume of 1 mL Diluent C) or transplanted without pre-labeling. Transplantation cell dose of $CD34^+$-enriched cells was: 0.5-1 $\times$ 10^6 cells/mouse; sorted $CD34^+CD38^{-/low}$ cells: 2 $\times$ 10^5 cells/mouse (Figure 1B, R2). Cells were recovered from the BM, spleen, or lungs of transplanted mice at time points as indicated and were analyzed for the presence of either $PKH26^+$ or human cells by flow cytometry acquiring 10^6 cells per sample (FACScalibur) (See right column, page 3284, Kollet et al., 2001).

Kollet et al. does not explicitly teaches (I) the limitation "exposing said stem cells to a matrix metalloprotease or an active portion thereof" recited in step (b) of claim 30, and (II) the limitation "wherein said exposing said stem cells to said matrix metalloprotease or said active portion thereof, is effected by: (i) expressing a polynucleotide encoding said matrix

metalloprotease or said active portion thereof in said stem cells; and/or (ii) contacting said stem cells with said matrix metalloprotease or said active portion thereof, as recited in claim 38.

Janowska-Wieczorek et al. teaches that peripheral blood CD34(+) cells, regardless of whether they were mobilized or not, strongly expressed both gelatinases (MMP-2 and MMP-9) in contrast to steady-state bone marrow CD34(+) cells, which did not. However, all the growth factors and cytokines tested could induce MMP-2 and MMP-9 secretion by the latter cells. Moreover, the stimulatory effects of G-CSF and SCF on both MMP-2 and MMP-9 secretion were found to be significantly higher in CD34 (+) cells isolated from bone marrow than in those from peripheral blood.

It is worth noting that Kollet et al. teaches isolated $CD34^+$ cells incubated with RPMI supplemented with stem cell factor (SCF) and Janowska-Wieczorek et al. teaches stimulatory effects of SCF on secretion MMP-2 and MMP-9 secretion. Based on the teachings of Janowska-Wieczorek et al., CD34+ cells inherently expresses and secret gelatinases (MMP-2 and MMP-9) either in the absent or in the presence of induction by growth factors or cytokines. Therefore, a cell population comprising population of $CD34^+$ or sub-population of $CD34^+CD38^{-/low}$ hematopoietic stem cells taught by Kollet et al. are inherently exposed/contacted to the secreted MMP-2 and MMP-9 matrix metalloproteases that are expressed from the endogenous genes encoding MMP-2 and MMP-9 in the genome of the $CD34^+$ or $CD34^+CD38^{-/low}$ hematopoietic stem cells of the cell population.

Thus, Kollet et al. (2001), as evidenced by Janowska-Wieczorek et al. (1999), clearly anticipates claims 30-36, 38, and 39 of instant application.

3. Claims 30-36, 38, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by **Kollet et al.** (Kollet et al., The plant lectin FRIL supports prolonged in vitro maintenance of quiescent human cord blood CD34(+)CD38(-/low)/SCID repopulating stem cells, *Exp Hematol.* 28(6):726-36, 2000) as evidenced by **Janowska-Wieczorek et al.** (Janowska-Wieczorek et al., Growth factors and cytokines upregulate gelatinase expression in bone marrow CD34(+) cells and their transmigration through reconstituted basement membrane, *Blood*, 93(10):3379-90, 1999; this reference is listed as reference C31 in the IDS filed by Applicant on 01/29/2007).

Claim 30 is directed to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation.

Claim interpretation: The limitation "having CXCR4 levels above a predetermined threshold" recited in claim 30 is interpreted as any level of CXCR4 expression because "a predetermined threshold" can be any level of CXCR4 expression. The limitation "exposing said stem cells to a matrix metalloprotease or an active portion thereof" recited in claim 30 reads on exposure to (i) any amount of a matrix metalloprotease expressed by either exogenous or endogenous nucleic acid molecule of collected stem cells, or (ii) any amount of matrix metalloprotease polypeptide added exogenously to the collected stem cells.

Kollet et al. developed a functional *in vivo* assay for primitive human hematopoietic cells based on their ability to home to and repopulate the marrow of sub-lethally irradiated C.B-17, NOD/LtSz mice homozygous for the severe combined immunodeficiency $Prkdc^{scid}$ mutation and recently into NOD/SCID B_2M^{null} mice. In this assay, the human cells are injected intravenously and repopulate the murine bone marrow (BM). (See introduction, page 726, Kollet et al., 2000)

With regard to step (a) of claim 30 and limitations of claims 34-36, Kollet et al. teaches isolation of CD34+ hematopoietic stem cells from human cord blood (CB) sample using the MACS cell isolation kit and MidiMacs columns. $CD34^+CD38^{-/low}$ cells were purified by FACS sorting ($FACStar^+$) after staining enriched $CD34^+$ cells with mAb anti human CD34-FITC and anti human CD38 PE (purity > 99%) (See Materials and methods, right column, page 727, Kollet et al., 2000).

With regard to step (c) of claim 30 and limitation of claim 39, Kollet et al. teaches that $CD34^+CD38^{-/low}$ cells were purified by FACS sorting ($FACStar^+$) (See Materials and methods, left column, page 727, Kollet et al., 2000), and that engraftment and repopulation by $CD34^+CD38^{-/low}$ SRC (human SCID repopulating stem cells) is dependent on CXCR4 expression (See bridging paragraph, pages 726-727, Kollet et al., 2000), and $CD34^+CD38^{-/low}$ cells were purified by FACS sorting ($FACStar^+$).

With regard to the collecting stem cell effected by a surgical procedure recited in claim 31, Kollet et al. teaches that the human CD34+ enriched cells were injected into the tail vein of irradiated mice in 0.5 mL of RPMI with 10% FBS. Mice were sacrificed 1 month post-transplantation, and BM cells were flushed from the eight bones of each mouse (femurs, tibias,

humeri, and pelvis) representing about a third of the total marrow mass of the mouse. For secondary transplantation, cells from eight bones of primary transplanted recipients were flushed. Cells from three primary mice were pooled (to obtain the equivalent total cell numbers of one mouse) and transplanted into one NOD/SCID B_2M^{null} mouse. (See Materials and methods, right column, page 727, Kollet et al., 2000).

Kollet et al. does not explicitly teaches (I) the limitation "exposing said stem cells to a matrix metalloprotease or an active portion thereof" recited in step (b) of claim 30, and (II) the limitation "wherein said exposing said stem cells to said matrix metalloprotease or said active portion thereof, is effected by: (i) expressing a polynucleotide encoding said matrix metalloprotease or said active portion thereof in said stem cells; and/or (ii) contacting said stem cells with said matrix metalloprotease or said active portion thereof, as recited in claim 38.

Janowska-Wieczorek et al. teaches that peripheral blood CD34(+) cells, regardless of whether they were mobilized or not, strongly expressed both gelatinases (MMP-2 and MMP-9) in contrast to steady-state bone marrow CD34(+) cells, which did not. However, all the growth factors and cytokines tested could induce MMP-2 and MMP-9 secretion by the latter cells. Moreover, the stimulatory effects of G-CSF and SCF on both MMP-2 and MMP-9 secretion were found to be significantly higher in CD34 (+) cells isolated from bone marrow than in those from peripheral blood.

It is worth noting that Kollet et al. teaches isolated $CD34^+$ cultured in the presence of stem cell factor (SCF) (See second paragraph, left column, page 727, Kollet et al., 2000) and Janowska-Wieczorek et al. teaches stimulatory effects of SCF on secretion MMP-2 and MMP-9

secretion. Based on the teachings of Janowska-Wieczorek et al., CD34+ cells inherently expresses and secret gelatinases (MMP-2 and MMP-9) either in the absent or in the presence of induction by growth factors or cytokines. Therefore, a cell population comprising population of $CD34^+$ or sub-population of $CD34^+CD38^{-/low}$ hematopoietic stem cells taught by Kollet et al. are inherently exposed/contacted to the secreted MMP-2 and MMP-9 matrix metalloproteases that are expressed from the endogenous genes encoding MMP-2 and MMP-9 in the genome of the $CD34^+$ or $CD34^+CD38^{-/low}$ hematopoietic stem cells of the cell population.

Thus, Kollet et al. (2000), as evidenced by Janowska-Wieczorek et al. (1999), clearly anticipates claims 30-36, 38, and 39 of instant application.

Conclusion

4. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632